ANALYSIS OF ASSOCIATIONS OF ALLELES AND GENOTYPES OF POLYMORPHIC LOCI OF A RANGE OF CANDIDATE GENES WITH PHENOTYPIC VARIATIONS AT THE LEVEL OF INTELLIGENCE

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Abstract. No doubt that the identification of predisposition toward certain types of activities becomes essential, which will allow using additional educational technologies as early as possible, thereby contributing to the development of existing powers in individuals and, as a result, increasing the productivity of future endeavors. There has been conducted a molecular genetic study of the frequency distribution of alleles and genotypes of 15 polymorphic genes variants, those involved in the regulation of memory span, synaptic plasticity, and the functioning of neurotransmitter systems of the brain of 7th and 8th grade students. DNA samples recovered from peripheral blood lymphocytes of 197 adolescents (89 boys, 108 girls), served as the material for molecular genetic testing; the students of the Municipal Autonomous Educational Institution «Lyceum No. 42» of the city district of Ufa city of the Republic of Bashkortostan – none registered in medical records. Statistically significant associations were defined: on the «general activity» scale with polymorphic loci rs6265 of the *BDNF* gene, rs4680 in the *COMT* gene and rs1387923 of the *NTRK2* gene, on the «mathematical intelligence» scale – rs6265 of the *BDNF* gene, on the psychoticism scale – rs2710102 in the *CNTNAP2* gene, rs6280 in the *DRD3* gene, rs1018381 in the *DTNBP1* gene and rs1387923 in gene *NTRK2*, on the neuroticism scale – rs6675281 in the *DISC1* gene, on the «spatial intelligence» scale – rs6675281 in the *DISC1* gene and rs4971684 in the *NRXN1* gene, on the «extroversion» scale – rs2832407 in the *GRIK1* gene.

Keywords: polymorphic loci, association, cognitive functions, genes.

List of Abbreviations

DNA – deoxyribonucleic acid
PCR – polymerase chain reaction
ARC – Activity Regulated Cytoskeleton Associated Protein
BDNF – Brain Derived Neurotrophic Factor
CNTNAP2 – Contactin Associated Protein 2
COMT – Catechol-O-Methyltransferase
CTNNB1 – Catenin Beta 1
DRD2 – Dopamine Receptor D2
DRD3 – Dopamine Receptor D3
DRD4 – Dopamine Receptor D4
DTNBP1 – Dystrobrevin Binding Protein 1
GRIK1 – Glutamate Ionotropic Receptor Kainate Type Subunit 1
NRG1 – Neuregulin 1
NRXN1 – Neurexin 1
NTRK2 – Neurotrophic Receptor Tyrosine Kinase 2
SNAP25 – Synaptosome Associated Protein 25
SNP – Single Nucleotide Polymorphism

Introduction

The study of the productivity of cognitive functions being an integral part of mental health is becoming increasingly relevant today due to the increased requirements for effective intellectual activity in all spheres of community functioning. The choice of profession, despite the obvious responsibility of this step, is not always made correctly. No doubt that the identification of predisposition toward certain types of activities becomes essential, which will al-

low using additional educational technologies as early as possible, thereby contributing to the development of existing powers in individuals and, as a result, increasing the productivity of future endeavors.

One of the largest Russian psychologists S.L. Rubinstein defined the abilities as «a complex structure, a complex of mental properties that make a person suitable for a certain, historically formed type of socially useful professional activity. Every special ability is the capacity for something» (Rubinshtein, 2003). Life experience shows that in many challenging types of activities, individuals manage to achieve very high results. There is no doubt that in any complex activity there are specialists whose professional level is much higher than the average. It is crucial to note that giftedness in most cases manifests itself in only one field of activity - a talented poet is often absolutely incapable of mathematics, and a mathematician is only in rare cases can be a great athlete at the same time. Consequently, it can be claimed that there is the existence of special abilities for certain types of complex activities. Special abilities are anatomical and physiological features of the brain and the nervous system as a whole, individual variants of the structure of the cerebral cortex, its functionally mature separate areas. In common terms, these special characteristics are usually called talents. Special abilities are genetically determined, although the role of upbringing and education is extremely important for their reliable progress. For fruitful activity, an individual must have general abilities: positive personal qualities – diligence, self-organization, perseverance, and so on, as well as developed creativity and a sufficiently high general intelligence.

A little more than 10 years ago, a group of researchers proposed the theory of universal genes (universalist genes hypothesis), according to which the same gene may be involved in the formation or absence of a certain trait. It is considered that genes involved in the development of cognitive abilities will also be responsible for the formation of individual abilities (Plomin *et al*., 2007). These include genes involved in the regulation of working memory span (*DTNBP1, CTNNB1, GRIK1*), in the regulation of synaptic plasticity (*CNTNAP2, NRXN1, NRG1, DISC1, BDNF, NTRK2, ARC, SNAP25*), in the functioning of neurotransmitter systems of the brain (*5-HTT, DRD2, DRD4*).

We have conducted a molecular genetic study of the frequency distribution of alleles and genotypes of 15 polymorphic variants of genes involved in the regulation of working memory, synaptic plasticity, and the functioning of neurotransmitter systems of the brain of 7 and 8 grade students.

There has been carried out a comparative analysis of the frequency distribution of alleles and genotypes of these genetic variants in groups corresponding to low, medium and high indicators on the following scales: sensory abilities, spatial abilities, emotional and evaluative abilities, motor emotionality, intellectual emotionality, communicative emotionality, general activity, general emotionality, motor plasticity, intellectual plasticity, communicative plasticity, neuroticism, psychoticism, verbal intelligence, mathematical intelligence, spatial intelligence, general intelligence, memory.

Materials and Methods

Study populations

DNA samples recovered from peripheral blood lymphocytes of 197 adolescents (89 boys, 108 girls), served as the material for molecular genetic testing; the students of the Municipal Autonomous Educational Institution «Lyceum No. 42» of the city district of Ufa city of the Republic of Bashkortostan - none registered in medical records. All were students in grades 7 and 8.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research bioethical committee of the Institute of Biochemistry and Genetics, Ufa Federal Research Center of the Russian Academy of Sciences and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Each participant gave written informed consent.

Methods

A set of methods that makes it possible to compare the cognitive and personal characteristics of adolescents in a Russian sample with data from international studies: 1. Temperament structure questionnaire STQ-77, adult and adolescent versions – on-line. (In the works of I. Trofimova, a neurochemical substantiation of the components of the structure of temperament is presented); Personality questionnaire by R.B. Cattell ("Imaton", 2019), adolescent (14-PF) and adult (16-PF) versions - computer implementation; Amthauer Intelligence Structure Test ("Imaton", 2019); Test of diagnostics of cognitive style impulsiveness/reflexivity "Comparison of similar drawings" by J. Kagan (computer implementation in INT-testing software); associated with Encephalan. A set of methods for assessing the characteristics of thinking and cognitive-style regulation: 1. Methodology for diagnosing cognitive styles; 2. Methodology for diagnosing conceptual abilities; 3. Creative thinking test by E. Torrens); 4. Test of elementary logical operations - computer implementation in INT-testing software; associated with Encephalan. A set of methods for express assessments of individual mental resources in digital implementation: 1. Temperament; 2. Fundamental personality traits (PEN); 3. Character; 4. Motivation; 5. Cognitive styles; 6. Elementary logical operations

Genomic DNA was isolated from peripheral blood samples from ovarian cancer patients and controls by routine phenol-chloroform extraction. The DNA concentration was measured using NanoDrop 2000c UV-Vis Spectrophotometer (Thermo Fisher Scientific Inc., Waltham, MA, USA). Genotyping of polymorphic loci was performed using the technology of competitive allelic PCR at the final frequency - KASP (LLC «Maxim Medical», Moscow) using the PCR product detection system in the CFX96 time environment (Bio-Rad) (USA) and QuantStudio 12K Flex Real -Time PCR System (Thermo Fisher Scientific). This method uses allele-specific primers with a given end sequence, each of which includes one of two FRET (fluorescent resonance energy transfer) cassettes labeled with FAM or HEX dye. Amplification of the fragment occurs due to the competitive binding of allele-specific primers, with the calculation of sequences and the synthesis of new complementary sequences due to the universal reverse primer. Chi-square was used to test association and Hardy–Weinberg equilibrium (HWE) for each variant. All statistical assessments were two-sided and considered to be significant when p-value was < 0.05.

Results

The selection of polymorphic loci for the study was conducted on the basis of the following criteria: the presence of an association with the studied trait based on the results of previously conducted associative (including replicative) studies, the presence of an association with phenotypes having with the studied trait, common biological pathways, regulatory potential, influence on gene expression, association with non-synonymous substitutions, the frequency of polymorphism at of at least 5%. As a result, for further analysis, we selected 15 functionally significant polymorphic loci in the genes involved in the regulation of working memory span (*DTNBP1* (rs1018381), *CTNNB1* (rs3864004), *GRIK1* (rs2832407)), in the regulation of synaptic plasticity (*CNTNAP2* (rs2710102), *NRXN1* (rs4971684), *NRG1* (rs6994992), *DISC1* (rs6675281), *BDNF* (rs6265), *NTRK2* (rs1387923), *ARC* (rs2234911), *SNAP25* (rs363050)), in the functioning of neurotransmitter systems of the brain (*COMT* (rs4680), *DRD3* (rs6280), *DRD2* (rs1800497), *DRD4* (rs180955)).

There has been carried out a comparative analysis of the frequency distribution of alleles and genotypes of these genetic variants in groups corresponding to low, medium and high indicators on the following scales: sensory abilities, spatial abilities, emotional and evaluative abilities, motor emotionality, intellectual emotionality, communicative emotionality, general activity, general emotionality, motor plasticity, intellectual plasticity, communicative plasticity, neuroticism, psychoticism, verbal intelligence, mathematical intelligence, spatial intelligence, general intelligence, memory.

When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic loci rs2234911 in the *ARC* gene between children with low, medium and high indicators according to the scales described above, there were no differences revealed between the studied groups ($p > 0.05$).

We have shown that according to the multiplicative and general inheritance model, the allele G of the polymorphic locus rs6265 in the BDNF gene is associated with «low values» ($\chi2 = 5.79$; $p = 0.02$), the allele A – c «average values» ($\chi2 = 5.79$; $p = 0.02$), the genotype GG – c «high values» on the scale of «total activity» ($\chi2 = 4.52$; $p = 0.03$) (Tables 1, 2).

It was also established that according to the multiplicative inheritance model, the G allele of the polymorphic locus rs6265 in the BDNF gene is associated with «high values», the A – c allele with «low values» on the scale of «mathematical intelligence» ($\chi2 = 4.77$; $p = 0.03$) (Table 3).

It was found that the C allele and the CC genotype of the polymorphic locus rs2710102 in the *CNTNAP2* gene are associated with «high values» ($\chi2 = 4.57$; $p = 0.03$ and $\chi2 = 7.91$; $p = 0.02$, respectively), the T–c allele «low values» ($\chi2 = 4.57$; $p = 0.03$) and «medium values» ($\chi2 = 10.00$; $p = 0.002$), genotype TT and CT - c «mean values» ($\chi2 = 7.91$; $p = 0.02$) on the scale of «psychoticism» (Tables 4–6).

It is shown that the genotype GG of the polymorphic locus rs4680 in the *COMT* gene, according to the dominant inheritance model, is associated with «average values» on the scale of «total activity» (Table 7).

When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic loci rs3864004 in the *CTNNB1* gene between children with low, medium and high indicators according to the scales described above, there were no differences revealed between the studied groups ($p > 0.05$).

It was found that the C allele and the CC genotype of the polymorphic locus rs6675281 (Leu607Phe) in the *DISC1* gene are associated with «low values» ($\chi2 = 4.94$; $p = 0.03$ and $\chi2 = 7.91$; $p = 0.02$, respectively), the T allele with «average values» ($\chi2 = 4.94$; $p = 0.03$) according to the «neuroticism» scale (Tables 8, 9).

We also revealed statistically significant differences in the frequency distribution of alleles and genotypes for this locus on the «spatial intelligence» scale: the C allele and the CC genotype of the polymorphic locus rs6675281 in the *DISC1* gene are associated with «high values» ($\chi2 = 4.70$; $p = 0.03$ and $\chi2 = 4.53$; $p = 0.03$, respectively), T –c allele «low values» ($\chi2 = 4.70$; $p = 0.03$) (Tables 10, 11).

When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic locus rs1800497 in the *DRD2* gene between children with low, medium and high indicators according to the scales described above, there were no differences revealed between the studied groups ($p > 0.05$).

It was found that the C allele, CC and CT genotypes of the rs6280 polymorphic locus in the *DRD3* gene are associated with «average values» ($\chi2 = 5.66$; $p = 0.02$, $\chi2 = 6.14$; $p = 0.05$ and $\chi2 = 6.14$; $p = 0.05$, respectively), the T allele and TT – c genotype are «low values» on the scale of «psychoticism» ($\chi2 = 5.66$; $p = 0.02$ and $\chi2 = 6.14$; $p = 0.05$, respectively) (Tables 12, 13).

When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic locus rs180955 in the *DRD4* gene between children with low, medium and high indicators according to the scales described above, there were no differences revealed between the studied groups ($p > 0.05$).

It was shown that the T allele of the polymorphic locus rs1018381 in the *DTNBP1* gene is associated with «low values» ($\chi2 = 3.86$; $p = 0.05$), the T allele and the TT genotype - with «average values» ($\chi2 = 4.94$; $p = 0.03$ and $\chi2 = 6.43$; $p = 0.04$, respectively), the C allele, genotype CC and CT - with «high values» on the scale of «psychoticism» ($\chi2 = 4.94$; $p = 0.03$, $\chi2 = 6.43$; $p = 0.04$ and $\chi2 = 6.43$; $p = 0.04$, respectively) (Tables 14, 15, 16).

It was revealed that allele A of the polymorphic locus rs2832407 in the *GRIK1* gene is associated with «low values», allele C – with «high values» on the «extraversion» scale ($\chi2 = 4.07$; $p = 0.04$) (Table 17).

Table 1

Comparative analysis of the frequency distribution of the allele frequencies of the rs6265 polymorphic locus in the *BDNF* gene between the groups «low values» and «average values» according to the multiplicative model of inheritance according to the «general activity» scale

Alleles	low values	average values	χ^2	*p*	*OR*	
	n = 37	n = 71			value	95% CI
A	0.068	0.190	5.79	0.02*	0.31	0.11 – 0.84
G	0.932	0.810			3.24	1.19 – 8.81

Note: * Statistically significant differences (Tables 1-22)

Table 2

Comparative analysis of the frequency distribution of the genotypes of the rs6265 polymorphic locus in the *BDNF* gene between the groups «low values» and «average values» according to the recessive model of inheritance according to the «general activity» scale

Genotypes	low values	average values	χ^2	*p*	*OR*	
	n = 37	n = 71			value	95% CI
AA+AG	0.135	0.324	4.52	0.03*	0.33	0.11 – 0.95
GG	0.865	0.676			3.07	1.06 – 8.90

Table 3

Comparative analysis of the frequency distribution of allele frequencies of the rs6265 polymorphic locus in the *BDNF* gene between the groups «low values» and «high values» according to the multiplicative model of inheritance according to the «mathematical intelligence» scale

Alleles	low values	high values	χ^2	*p*	*OR*	
	n = 37	n = 20			value	95% CI
A	0.203	0.050	4.77	0.03*	4.83	1.05 – 22.32
G	0.797	0.950			0.21	0.04 – 0.96

Table 4

Comparative analysis of the distribution of allele frequencies of the rs2710102 polymorphic locus in the *CNTNAP2* gene between the groups «low values» and «high values» according to the multiplicative model of inheritance according to the «psychoticism» scale

Alleles	low values	high values	χ^2	*p*	*OR*	
	n = 44	n = 19			value	95% CI
C	0.477	0.684	4.57	0.03*	0.42	0.19 – 0.94
T	0.523	0.316			2.37	1.06 – 5.29

Table 5

Comparative analysis of the distribution of allele frequencies of the rs2710102 polymorphic locus in the *CNTNAP2* gene between the groups of «average values» and «high values» according to the multiplicative model of inheritance according to the «psychoticism» scale

Alleles	average values	high values	χ^2	*p*	*OR*	
	n = 80	n = 19			value	95% CI
C	0.400	0.684	10.00	0.002*	0.31	0.14 – 0.65
T	0.600	0.316			3.25	1.53 – 6.91

Table 6

Comparative analysis of the distribution of frequencies of the genotypes of the rs2710102 polymorphic locus in the *CNTNAP2* gene between the groups «average values» and «high values» according to the general model of inheritance according to the «psychoticism» scale

Genotypes	average values	high values	χ^2	*p*	*OR*	
	n = 80	n = 19			value	95% CI
C C	0.225	0.526	7.91	0.02*	0.26	0.09 – 0.74
C T	0.350	0.316			1.17	0.40 – 3.40
T T	0.425	0.158			3.94	1.06 – 14.62

Table 7

Comparative analysis of the frequency distribution of the genotypes of the rs4680 polymorphic locus in the COMT 2 gene between the groups «average values» and «high values» according to the dominant model of inheritance according to the «general activity» scale

Genotypes	average values	high values	χ^2	*p*	*OR*	
	n = 78	n = 21			value	95% CI
AA+AG	0.218	0.429	3.79	0.05*	0.37	0.13 – 1.03
GG	0.782	0.571			2.69	0.97 – 7.45

Table 8

Comparative analysis of the distribution of allele frequencies of the polymorphic locus rs6675281 in the *DISC1* gene between the groups «low values» and «average values» according to the multiplicative model of inheritance according to the «neuroticism» scale

Alleles	low values	average values	χ^2	*p*	*OR*	
	n = 45	n = 24			value	95% CI
T	0.078	0.208	4.94	0.03*	0.32	0.11 – 0.91
C	0.922	0.792			3.12	1.10 – 8.82

Table 9

Comparative analysis of the frequency distribution of the genotypes of the rs6675281 polymorphic locus in the *DISC1* gene between the groups «low values» and «average values» according to the recessive model of inheritance according to the «neuroticism» scale

Genotypes	low values	average values	χ^2	*p*	*OR*	
	n = 45	n = 24			value	95% CI
TT+TC	0.133	0.417	7.05	0.008*	0.22	0.07 – 0.70
CC	0.867	0.583			4.64	1.42 – 15.14

Table 10

Comparative analysis of the distribution of allele frequencies of the polymorphic locus rs6675281 in the DISC1 gene between the groups «low values» and «high values» according to the multiplicative model of inheritance according to the «spatial intelligence» scale

Alleles	low values	high values	χ^2	*p*	*OR*	
	n = 46	n = 20			value	95% CI
T	0.109	0.000	4.70	0.03*	10.31	0.59 – 180.36
C	0.891	1.000			0.10	0.01 – 1.70

Table 11

Comparative analysis of the frequency distribution of the genotypes of the polymorphic locus rs6675281 in the DISC1 gene between the groups «low values» and «high values» according to the dominant model of inheritance according to the «spatial intelligence» scale

Genotypes	low values	high values	χ^2	*p*	*OR*	
	n = 46	n = 20			value	95% CI
TT+TC	0.196	0.000	4.53	0.03*	10.39	0.57 – 187.71
CC	0.804	1.000			0.10	0.01 – 1.74

Table 12

Comparative analysis of the distribution of allele frequencies of the rs6280 polymorphic locus in the *DRD3* gene between the groups «low values» and «average values» according to the multiplicative model of inheritance according to the «psychoticism» scale

Alleles	low values	average values	χ^2	*p*	*OR*	
	n = 44	n = 81			value	95% CI
C	0.170	0.309	5.66	0.02*	0.46	0.24 – 0.88
T	0.830	0.691			2.17	1.14 – 4.15

Table 13

Comparative analysis of the frequency distribution of the genotypes of the rs6280 polymorphic locus in the *DRD3* gene between the groups «low values» and «average values» according to the general model of inheritance according to the «psychoticism» scale

Genotypes	low values	average values	χ^2	*p*	*OR*	
	n = 44	n = 81			value	95% CI
C C	0.023	0.074	6.14	0.05*	0.29	0.03 – 2.50
C T	0.295	0.469			0.47	0.22 – 1.04
T T	0.682	0.457			2.55	1.18 – 5.51

Table 14

Comparative analysis of the distribution of frequencies of alleles of the polymorphic locus rs1018381 in the *DTNBP1* gene between the groups «low values» and «high values» according to the multiplicative model of inheritance according to the «psychoticism» scale

Alleles	low values	average values	χ^2	*p*	*OR*	
	n = 44	n = 20			value	95% CI
T	0.920	0.800	3.86	0.05*	2.89	0.97 – 8.64
C	0.080	0.200			0.35	0.12 – 1.03

Table 15

Comparative analysis of the frequency distribution of the allele frequencies of the polymorphic locus rs1018381 in the *DTNBP1* gene between the groups «average values» and «high values» according to the multiplicative model of inheritance according to the «psychoticism» scale

Alleles	average values	high values	χ^2	*p*	*OR*	
	n = 81	n = 20			value	95% CI
T	0.920	0.800	4.94	0.03*	2.87	1.10 – 7.48
C	0.080	0.200			0.35	0.13 – 0.91

Table 16

Comparative analysis of the frequency distribution of the genotypes of the polymorphic locus rs1018381 in the *DTNBP1* gene between the groups «average values» and «high values» according to the general inheritance model according to the «psychoticism» scale

Genotypes	average values	high values	χ^2	*p*	*OR*	
	n = 81	n = 20			value	95% CI
TT	0.840	0.650	6.43	0.04*	2.82	0.94 – 8.41
TC	0.160	0.300			0.45	0.14 – 1.37
CC	0.000	0.050			0.08	0.00 – 2.03

Table 17

Comparative analysis of the distribution of allele frequencies of the rs2832407 polymorphic locus in the *GRIK1* gene between the groups «low values» and «high values» according to the multiplicative model of inheritance according to the «extaversion» scale

Alleles	low values	high values	χ^2	*p*	*OR*	
	n = 45	n = 22			value	95% CI
A	0.378	0.205	4.07	0.04*	2.36	1.01 – 5.51
C	0.622	0.795			0.42	0.18 – 0.99

When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic locus rs6994992 in the *NRG1* gene between children with low, medium and high indicators according to the scales described above, there were no differences revealed between the studied groups ($p > 0.05$).

It is shown that allele C, genotypes CC and CT of polymorphic locus rs4971684 in the *NRXN1* gene are associated with «high values» ($\chi2 = 6.42$; $p = 0.01$ and $\chi2 = 7.33$; $p = 0.03$, respectively), allele T, genotype TT – with «low values» on the scale of «spatial intelligence» ($\chi2 = 6.42$; $p = 0.01$ for alleles and $\chi2 = 7.33$; $p = 0.03$ for genotypes, respectively) (Tables 18, 19).

When analyzing the polymorphic locus rs1387923 in the *NTRK2* gene, statistically significant differences in the frequency distribution of alleles and genotypes were found between the groups with low, medium and high indicators on the «total activity» scale: allele C, genotypes CC and CT of the polymorphic locus rs1387923 in the *NTRK2* gene are associated with «low values», allele T, genotype TT – with «average values» ($\chi2 = 5.48$; $p = 0.02$ for alleles and $\chi2 = 11.73$; $p = 0.003$ for genotypes, respectively) (Tables 20, 21). We also found that the TT genotype of the polymorphic locus rs1387923 in the NTRK2 gene according to the recessive inheritance model is associated with «low values» on the scale of «psychoticism» ($\chi2 = 4.73$; $p = 0.03$) (Table 22).

Table 18

Comparative analysis of the distribution of allele frequencies of the polymorphic locus rs4971684 in the NRXN1 gene between the groups «low values» and «high values» according to the multiplicative model of inheritance according to the «spatial intelligence» scale

Alleles	low values	high values	χ^2	*p*	*OR*	
	n = 43	n = 22			value	95% CI
C	0.116	0.295	6.42	0.01*	0.31	0.12 – 0.79
T	0.884	0.705			3.19	1.26 – 8.03

Table 19

Comparative analysis of the frequency distribution of the genotypes of the polymorphic locus rs4971684 in the NRXN1 gene between the groups «low values» and «high values» according to the general model of inheritance according to the «spatial intelligence» scale

Genotypes	low values	high values	χ^2	*p*	*OR*	
	n = 43	n = 22			value	95% CI
C C	0.000	0.045	7.33	0.03*	0.16	0.01 – 4.22
C T	0.233	0.500			0.30	0.10 – 0.91
T T	0.767	0.455			3.96	1.32 – 11.87

Table 20

Comparative analysis of the distribution of allele frequencies of the polymorphic locus rs1387923 in the *NTRK2* gene between the groups «low values» and «average values» according to the multiplicative model of inheritance according to the «general activity» scale

Alleles	low values	average values	χ^2	*p*	*OR*	
	n = 42	n = 80			value	95% CI
C	0.595	0.438	5.48	0.02*	1.89	1.11 – 3.23
T	0.405	0.563			0.53	0.31 – 0.90

Table 21

Comparative analysis of the frequency distribution of the genotypes of the polymorphic locus rs1387923 in the *NTRK2* gene between the groups «low values» and «average values» according to the general model of inheritance on the scale «general activity»

Genotypes	low values	average values	χ^2	*p*	*OR*	
	n = 42	n = 80			value	95% CI
C C	0.262	0.225	11.73	0.003*	1.22	0.51 – 2.90
C T	0.667	0.425			2.71	1.24 – 5.90
T T	0.071	0.350			0.14	0.04 – 0.50

Table 22

Comparative analysis of the frequency distribution of the genotypes of the polymorphic locus rs1387923 in the *NTRK2* gene between the groups «low values» and «average values» according to the recessive inheritance model according to the «psychoticism» scale

Genotypes	low values	average values	χ^2	*p*	*OR*	
	n = 44	n = 20			value	95% CI
C C +CT	0.636	0.900	4.73	0.03*	0.19	0.04 – 0.95
T T	0.364	0.100			5.14	1.05 – 25.09

Discussion

The *ARC* protein is often examined by scientists studying the educatory process and operation of memory, as the activity of the Arc gene in mammalian nerve cells is essential for memorizing new information. Disruptions of the expression of this gene are observed in some psychopathologies characterized by cognitive deficits (Wang *et al*., 2013; Pastuzyn *et al*., 2018). When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic locus rs2234911 in the *ARC* gene between children with low, medium and high indicators according to the scales described above, no differences between the studied groups were revealed.

Brain-derived neurotrophic factor (*BDNF*) is an important signaling protein involved in the regulation of neurogenesis, growth and survival of neurons in the central nervous system. At the same time, BDNF deficiency reduces the plasticity of neurons, disrupts memory and learning ability, cognitive abilities (Tyler & Pozzo-Miller, 2001). One of the most studied loci of the *BDNF* gene is rs6265 (c.196G>A; Val66Met). We have shown that according to the multiplicative and general inheritance model, the allele G of the polymorphic locus rs6265 in the *BDNF*

gene is associated with «low values», the allele A – with «average values», the genotype GG – with «high values» on the scale of «total activity». It was also revealed that, according to the multiplicative inheritance model, the G allele of the polymorphic locus rs6265 in the *BDNF* gene is associated with «high values», the A allele with «low values» on the scale of «mathematical intelligence». Studies conducted on hippocampal cell cultures demonstrate a decrease in *BDNF* secretion in the presence of the rs6265*A allele in the structure corresponding to the amino acid methionine. The authors also demonstrated that this allele is associated with impaired episodic and working memory, as well as hippocampal function (Egan *et al.*, 2003). A 2018 meta-analysis conducted by Yue-Long Xu and colleagues showed that the G allele of the studied locus may be associated with the risk of epilepsy progression among the Asian population (Xu *et al*., 2018). There is the evidence of a decrease in the concentration of *BDNF* in people with increased anxiety and depression (Hwang *et al*., 2007).

The *CNTNAP2* gene is involved in the regulation of linguistic functions and social behavior. In addition, variations in the number of representation and deletion of certain sections of this gene are often associated with mental deficiency, epilepsy, schizophrenia (Poot *et al*., 2010), autism spectrum disorders, specific selective mutism. Through the use of functional magnetic resonance imaging (fMRI) method, the significance of the polymorphic variant rs2710102 in the *CNTNAP2* gene was shown: activation of prefrontal regions of the brain was observed in carriers of the «risky» allele in response to a linguistic task (Whalley *et al*., 2011). In our study, it was found that the C allele and the CC genotype of the polymorphic locus rs2710102 in the *CNTNAP2* gene are associated with «high values», the T allele –with «low values» and «average values», the TT and CT genotype -with «average values» on the «psychoticism» scale. There is the evidence in the literature that using the method of functional magnetic resonance imaging (fMRI), the significance of the polymorphic variant rs2710102 in the *CNTNAP2* gene was shown: activation of prefrontal regions of the brain was observed in carriers of a «risky» allele in response to a linguistic task (Whalley *et al*., 2011). In a recent study, there was shown that individuals with a homozygous CC genotype have a smaller volume of the left superior temporal gyrus (STG)/insula compared to the carriers of the T-allele. The authors speak about the indirect influence of *CNTNAP2* rs2710102 genotypes on social activity, mediated by the volume of the cerebral cortex STG/insula and parahippocampus. These findings allow us to understand the genetic effect of *CNTNAP2* variants on social behavior that can be regulated by the temporal cortex (Li *et al*., 2020).

The catechol-O-methyltransferase gene (*COMT*, 22q11) encodes an enzyme whose main function is the elimination of biologically active catecholamines. As other synoptic dopamine regulators (e.g. dopamine transporters) are rare in the prefrontal cortex, *COMT* plays a central role in regulating prefrontal dopamine levels (Meyer-Lindenberg *et al*., 2006). By now, the most studied polymorphic locus in the *COMT* gene is the highly functional polymorphic locus Val158Met (rs4680) in the 4th exon of the gene: replacing valine with methionine has an effect on the thermal stability of catechol-O-methyltransferase and can reduce its enzymatic activity in the human brain by 2 times (Chen *et al*., 2004). Thus, carriers of the Val allele will have a higher rate of dopamine degradation and, consequently, a decrease in its amount in synapses compared to carriers of the Met allele (Dickinson *et al*., 2009). In our study, it was shown that the GG genotype of the polymorphic locus rs4680 in the *COMT* gene is associated according to the dominant inheritance model with «average values» on the «total activity» scale. Previously, this polymorphic locus was associated with working memory, attentiveness control and cognitive functions of the brain (Aguilera *et al*., 2008).

Another important link in the regulation of working memory and related processes is β-catenin (encoded by the *CTNNB1* gene) – a highly conserved protein that performs many functions in the body, participating in the wnt signaling pathway. The latter is one of the intra-

cellular signaling pathways of animals that regulate embryogenesis, cell differentiation and the development of malignant tumors. Additionally, β-catenin is a cell adhesion molecule and participates in the regulation of synaptic plasticity, migration and growth of neurites in complex with cadherin, a cell adhesion molecule (Tucci *et al.*, 2014). When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic locus rs3864004 in the *CTNNB1* gene between children with low, medium and high indicators according to the scales described above, no differences between the studied groups were revealed.

The *DISC1* gene encodes a protein involved in the growth of neurites and the development of the cortex through interaction with other proteins. Translocation t (1; 11) (q42.1; q14.3) was described for this gene in related schizophrenia patients and in a big family in Scotland. There were characterized thr alternative variants of transcriptional splicing encoding different isoforms. There is data that the aberrant expression of *DISC 1* in astrocytes can disrupt the bioenergetics of astrocytes, resulting in abnormalities of synaptic neurotransmission and cognitive function in a region-dependent manner (Spalek *et al*., 2016). In our study, it was found that the C allele and the CC genotype of the polymorphic locus rs6675281 (Leu607Phe) in the *DISC1* gene are associated with «low values», the T allele with «average values» on the "neuroticism" scale. We also revealed statistically significant differences in the frequency distribution of alleles and genotypes for this locus on the "spatial intelligence" scale: the C allele and the CC genotype of the polymorphic locus rs6675281 in the *DISC1* gene are associated with «high values», the T allele with «low values». The literature describes associations of the polymorphic locus rs6675281 in the *DISC1* gene with various psychological signs and pathologies. Thus, in a research in France, it was found that the C allele is associated with the risk of schizophrenia progression (OR = 2.3, 95%, (CI) = 1.1–4.4) Another work by researchers from Iran shows the great role of the *DISC1* gene as a locus of susceptibility to attention deficit hyperactivity disorder (ADHD) and indicates that rs6675281 polymorphism is a factor of predisposition to ADHD in children (Kayyal *et al*., 2015).

Dopamine is synthesized in a rate-limiting reaction catalyzed by tyrosine hydroxylase (TH) and interacts with 5 different types of receptors (D1-D5): receptors of the D1 family (D1 and D5) stimulate the formation of cAMP, while receptors of the D2 family (D2, D3 and D4) inhibit this process. The *DRD2* (11q23) gene is probably involved in the formation of such temperament qualities as «novelty seeking», impulsivity, aggression. When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic locus rs1800497 in the *DRD2* gene between children with low, medium and high indicators according to the scales described above, no differences between the studied groups were revealed.

The *DRD3* gene encodes nbT D3 of five (D1-D5) dopamine receptors. The activity of the D3 subtype receptor is mediated by T proteins that inhibit adenylate cyclase. This receptor is located in the limbic regions of the brain, which are associated with cognitive, emotional and endocrine functions. We found that allele C, genotypes CC and CT of polymorphic locus rs6280 in the *DRD3* gene are associated with «average values», allele T and genotype TT – with «low values» on the scale of «psychoticism». The genetic variability of this gene may be associated with a predisposition to hereditary essential tremor type 1. Alternative splicing of this gene leads to transcript variants encoding different isoforms (Li *et al*., 2020). One of the most interesting for research is the polymorphic locus rs6280, also known as Ser9Gly, rs6280 allele (C) encodes glycine, and allele (T) encodes serine. In a study of 88 patients treated for schizophrenia with olanzapine, carriers of the rs6280 homozygous genitype (CC), had a higher positive remission of symptoms compared to carriers of CT or TT genotypes (13.8%; P = 0.033) (Yildiz *et al.*, 2015).

The dopamine D4 receptor is widely expressed in the central nervous system, especially in the frontal cortex, hippocampus,

amygdala and hypothalamus. The dopamine receptor D4 *DRD4* gene is located on chromosome 11p15.5 and has a very variable number of tandem repeats in the coding sequence (Bellgrove *et al*., 2003). The polymorphism is a 48-bp VNTR sequence in exon 3 encoding the third intracellular loop of the D4 receptor. The most common polymorphic variants of the receptor are D4.7 and D4.4. Individuals with repeats of D4.7 demonstrate both reduced binding affinity and receptor density for dopamine neurotransmission. The D4.7 allele correlates with impulsivity and lower levels of response inhibition (Eisenberg *et al*., 2007). Several studies have analyzed the relationship between the D4.7-repeat allele in the *DRD4* gene and attention deficit hyperactivity disorder (ADHD) (Li *et al*., 2021). When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic locus rs180955 in the *DRD4* gene between children with low, medium and high indicators according to the scales described above, no differences between the studied groups were revealed.

The dysbindin gene (*DTNBP1*, 6p22.3) is expressed in cortical neurons, including pyramidal neurons, possibly it modulates functions dependent on working memory. In addition, there is evidence of significant expression of the dysbindin gene in glutamatergic synapses, regulating the activity of neurons associated with working memory (Wolf *et al*., 2011). In our work, the T allele of the polymorphic locus rs1018381 in the *DTNBP1* gene is associated with «low values», the T allele and the TT genotype – with «average values», the C allele, the genotype CC and CT - with «high values» on the scale of «psychoticism». The results of the meta-analysis also confirm the involvement of polymorphic loci in the *DTNBP1* gene (rs1018381 and rs2719522) in the development of working memory, intelligence (Karlsgodt *et al*., 2011) and a number of mental diseases (schizophrenia, bipolar disorder, unipolar depression) (Zhang *et al*., 2010).

The gene of the ionotropic kainate glutamate receptor (*GRIK1*) encodes a subunit of the CluK1 receptor necessary for the transmission of astroglia–neuron signals in a hippocampus, where glutamate released from astroglia signals inhibitory neurons precisely due to the activation of neuronal kainate receptors (Alberdi *et al*., 2006). In this study, the polymorphic locus rs2832407 of the *GRIK1* gene was studied. We found that allele A of the polymorphic locus rs2832407 in the *GRIK1* gene is associated with «low values», allele C – with «high values» on the «extraversion» scale. According to the results of CWAS, the *GRIK1* gene is involved in the regulation of cognitive functions of the brain involved in the formation of mathematical abilities. Earlier it was reported that the minor allele of this polymorphic locus reduces the expression of the *GRIK1* gene (Docherty *et al*., 2010).

According to the literature, the neuregulin gene (*NRG1*) is associated with variations in the level of intelligence, cognitive abilities both in normal condition and in various mental illnesses. In our work, the polymorphic locus of the *NRG1* gene was considered: rs6994992. There is data that rs6994992 is a functional locus located in the 5'- UTR region of the *NRG1* gene, polymorphic variants of which determine differences in the activity of the *NRG1* gene promoter (Douet *et al*., 2014). When conducting a comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic locus rs6994992 in the *NRG1* gene between children with low, medium and high indicators according to the scales described above, no differences between the studied groups were revealed.

Neurexin 1 is a cell adhesion molecule and is an important modulator of neuronal processes such as maturation and differentiation of neurons, as well as synaptic plasticity (Zhang *et al*., 2013). Numerous studies have been conducted that have shown an association of reading frame shift mutations and missense mutations in the neurexin 1 gene (*NRXN1*, 2p16.3) with a wide range of neurocognitive disorders, including autism, Alzheimer's disease, mental retardation and schizophrenia (Jenkins *et al*., 2014). The *NRXN1* gene is characterized by a large number of polymorphic loci. We have shown that allele C, genotypes CC and CT of polymorphic locus rs4971684 in the *NRXN1*

gene are associated with «high values» ($\chi 2$ = = 6.42; p = 0.01 and $\chi 2$ = 7.33; p = 0.03, respectively), allele T, genotype TT – with «low values» on the scale of «spatial intelligence». A large number of literature data suggests engagement of neurexin 1 gene (*NRXN1*) in the development of a number of disorders characterized by cognitive deficits: autism spectrum disorders, schizophrenia, developmental delay and mental retardation (Enikeeva, 2008).

At present, there are many studies demonstrating the connection of the TrkB receptor gene (*NTRK2*, 9q22.1) with the development of a number of mental conditions and affective disorders (Spalek *et al.*, 2016). Studies conducted on model animals indicate the involvement of the *NTRK2* gene in stress-mediated cognitive impairment. Thus, overexpression of the *NTRK2* gene is associated with a decrease in anxiety in mice, whereas inactivation of this gene led to learning disorders in stressful situations (Mirkovic *et al.*, 2016). When analyzing the polymorphic locus rs1387923 in the NTRK2 gene, we found statistically significant differences in the frequency distribution of alleles and genotypes between the group with low, medium and high indicators on the «total activity» scale: allele C, genotypes CC and CT of the polymorphic locus rs1387923 in the *NTRK2* gene are associated with «low values», allele T, genotype TT – with «average values». We also found that the TT genotype of the polymorphic locus rs1387923 in the *NTRK2* gene, according to the recessive inheritance model, is associated with «low values» on the «psychoticism» scale. According to the data, the expression of the tyrosine kinase receptor (*NTRK2*) gene is most expressed in the regions of brain involved in the regulation of emotional behavior and cognitive processes (amygdala, caudate nucleus, cortex, hippocampus, hypothalamus, thalamus and other parts of the brain) (Enikeeva, 2008).

The genetic study results can be used in combination with psychological and psychophysiological tests to identify the predisposition of students to engage in certain types of activities.

Conflicts of interest: the authors declare no conflict of interest.

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